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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/289,290	08/11/1994	RALPH H. WEICHSELBAUM	ARCD:086/SER	1375

7590 01/19/2005

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 01/19/2005

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 08/289,290
Filing Date: August 11, 1994
Appellant(s): WEICHSELBAUM ET AL.

Edward P. Gamson
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed May 24, 2004.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

This appeal involves claims 29, 37, 40.

Claims 1-3, 6, 8-14,18-22, 26-29, 31-42 are currently pending in the application.

Claims 29 and 30 were on Remand by the decision of the Board of Patent Appeals and Interferences dated March 14, 2002.

Subsequently, Claim 30 has been canceled, and Claims 37-42 were submitted on November 12, 2002.

Claims 1-3, 6, 8-14, 18-22, 26-28, 31-36, 38, 39, 41, 42 are allowable in view of the decision of the Board of Patent Appeals and Interferences dated March 14, 2002.

Claims 29, 37, and 40 are currently rejected, and on appeal.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief with respect to the product claims (29 and 37) is correct.

The summary of invention contained in the brief with respect to the process claim (40) is inaccurate concerning step (b), the dosing of ionizing radiation, which will be discussed in detail in the rejection under 35 U.S.C. § 112, 1st paragraph below.

(6) Issues

The appellant's statement of the issues in the brief is substantially correct with regard to issues (A), (B), (C), and (D).

Upon further consideration, the following rejections are withdrawn:

1. Previous rejection of Claims 29 and 37 under 35 U.S.C. § 102(e) as being anticipated by *Connelly et al* (US 5,935,935), is withdrawn.
2. Previous rejection of Claim 29 under 35 U.S.C. § 102(e) as being anticipated by *Glorioso et al* (US 6,228,356), is withdrawn

Currently, Claim 40 stands rejected under 35 U.S.C. 112, first paragraph for new matter; and Claims 29 and 37 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Zhang et al* (US6,143,290), in view of *Walther et al* (Anticancer Res 1993 Sept;13:1565-74).

(7) Grouping of Claims

Appellant's brief includes a statement that for each ground of rejection, the rejected claims do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

6143290 Zhang et al. November 7, 2000

Walther et al, Anticancer Res. 1993;13:1565-74.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim 40 stands rejected under 35 U.S.C. 112 first paragraph, because the specification as originally filed does not describe the invention as now claimed.

Given the broadest reasonable interpretation, Claim 40 as written encompasses administering to a host a one-time dose of ionizing radiation at between 50-70 Gray (Gy), The original disclosure fails to specify such a one-time dosing regimen as now claimed, thus this dosing regimen is now considered to be new matter.

MPEP 2163.02 states that "WHENEVER THE ISSUE ARISES, THE FUNDAMENTAL FACTUAL INQUIRY IS WHETHER A CLAIM DEFINES AN INVENTION THAT IS CLEARLY CONVEYED TO THOSE SKILLED

IN THE ART AT THE TIME THE APPLICATION WAS FILED...IF A CLAIM IS AMENDED TO INCLUDE SUBJECT MATTER, LIMITATIONS, OR TERMINOLOGY NOT PRESENT IN THE APPLICATION AS FILED, INVOLVING A DEPARTURE FROM, ADDITION TO, OR DELETION FROM THE DISCLOSURE OF THE APPLICATION AS FILED, THE EXAMINER SHOULD CONCLUDE THAT THE CLAIMED SUBJECT MATTER IS NOT DESCRIBED IN THAT APPLICATION". In the instant case, the original disclosure describes the dose of ionizing radiation as 2 Gy/day to a total dose of 50 to 70 Gy in example VI, page 42; or between 5-20Gy in example VIII, pages 47-48. According to the original disclosure, the total accumulative doses of 50 to 70 Gy are administered at 2Gy daily in a period ranging from 25 to 35 days; which significantly differs from a one-time dose between 50 to 70 Gy. Thus the original disclosure differs from currently claimed dose range. Such difference may have significant impact on the physiological condition of the recipient and therapeutic effect. Thus, it is concluded that the amendment is a departure from or an addition to the disclosure of the application as filed, accordingly, it introduces new matter into the disclosure.

For reasons set forth above, the amendment filed 11/12/2002 stands objected to under 35 U.S.C. §132 because it introduces new matter into the disclosure. 35 U.S.C. §132 states that no amendment shall introduce new matter into the disclosure of the invention.

To the extent that the claimed method is not adequately described in the instant disclosure, claim 40 stands rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to

make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been properly described, and is not conventional in the art.

Claims 29 and 37 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Zhang et al* (US6,143,290), in view of *Walther et al* (Anticancer Res 1993 Sept;13:1565-74).

Claim 29 is drawn to a pharmaceutical composition comprising a genetic construct comprising a nucleic acid that encodes a tumor necrosis factor alpha (TNF-α) operatively linked to a constitutive promoter dispersed in a pharmacologically acceptable carrier, wherein the genetic construct is packaged within an adenovirus particle.

Claim 37 further limits the adenoviral particle as containing a deletion of the E1 and/or E3 region of the adenoviral genome.

Zhang et al teach an adenovirus construct comprising a nucleic acid that encodes a tumor suppressor gene p53, which may be packaged in virions (e.g. abstract and the last paragraph in column 2), and which lacks a E1 or E3 region (column 4, lines 33-43). *Zhang et al* go on to teach that the p53 expression region is under the control of a strong constitutive promoter such as a CMV promoter or SV40 (column 3, lines 64-66), and is dispersed in a pharmaceutically acceptable solution or buffer (column 5, lines 1-5). *Zhang et al* also teach the particular advantages of an adenovirus system as compared to other art-known vectors such as retroviral vectors, which include the ability to carry large pieces of foreign DNA, the structural stability, the broad target range, the

lack of any known association with cancers, and the relative easy to produce and high infectivity (e.g. the paragraph bridging columns 11 & 12). They go on to teach the need to develop strategies for replacing or alternative to a retroviral vector. To this end, *Zhang et al* state, "MAJOR PROBLEMS ARE ASSOCIATED WITH USING RETROVIRAL VECTORS FOR GENE THERAPY SINCE THEIR INFECTIVITY DEPENDS ON THE AVAILABILITY OF RETROVIRAL RECEPTORS ON THE TARGET CELLS, THEY ARE DIFFICULT TO CONCENTRATE AND PURIFY, AND THEY ONLY INTEGRATE EFFICIENTLY INTO REPLICATING CELLS", "THERE REMAINS, THEREFORE, A CLEAR NEED FOR THE DEVELOPMENT OF NEW METHODS FOR INTRODUCING TUMOR SUPPRESSOR GENES, SUCH AS P53, INTO CELLS" (column 2, lines 31-55). The teaching of *Zhang et al* differs from instant claimed in that they disclose an adenoviral vector comprising a nucleic acid that encodes a tumor suppressor p53, not TNF-α.

Walther et al supplemented the teaching of *Zhang et al* by establishing that it is well known in the art a gene therapy vector could be used for encoding and expressing TNF-α for the treatment of tumor. *Walther et al* teach a genetic construct comprising a nucleic acid that encodes TNF-α packaged in a retrovirus particle (paragraph bridging page 1565-66, and 2nd paragraph in left column of 1566). They introduce the recombinant retrovirus into tumor cells causing constitutive expression of TNF-α and reduction of tumor growth (abstract). *Walther et al* teach that compared to the external addition of TNF-α, endogenous expression of TNF-α could use much lower dose yet achieve similar effect, which would reduce the side effect of the anti-tumor agent TNF-α. Although *Walther et al* do not teach an adenoviral vector, the vector and the need to use it in place of a retroviral vector was taught by *Zhang et al*.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the vectors taught by *Zhang et al* and *Walther et al* by simply using an adenoviral vector for expressing TNF-α with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the advantages of adenoviral vectors as compared to the retroviral viral vectors are taught by *Zhang et al.* Further given the effectiveness in killing tumor cells using both the retroviral vector as taught by *Walther et al* and the adenoviral vector as taught by *Zhang et al*, the ordinary skilled in the art would have had a reasonable expectation of success of making and using the recombinant adenoviral vector as taught by *Zhang et al* for expressing the TNF-α as taught by *Walther et al* for tumor suppression. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

(11) Response to Argument

Appellant's arguments have been addressed as they apply to the current standing rejections and in the order in which they have been presented in the appellant's second corrected Brief on Appeal.

Arguments concerning the rejection of Claims 29 and 37 under 35 U.S.C. 103(a) as being unpatentable over *Zhang et al.* in view of *Walther et al.*

The appellant argues that the Office does not provide any basis for one of ordinary skill in the art to modify the disclosure of the Zhang patent and the Walther

paper in a significant manner except perhaps after reading the present disclosure and using hind sight. The appellant argues one would have to (a) ignore the Zhang patent teaching of decreased p53 expression observed using the adenoviral vector, (b) ignore the Walther paper's teaching of tumor growth inhibition associated with constitutive expression of retrovirally-encoded TNF-α to arrive at presently claimed invention.

In response to appellant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, the Office relied only on the knowledge that was available to the ordinary skill at the time the claimed invention was made. Such could be seen in the teaching of *Zhang et al*, who clearly teach the motivation why one would use an adenoviral vector in place of a retroviral vector for expressing a therapeutic gene as cited *supra,* i.e. high gene transfer efficiency, broad target range, and non-tumorogenicity of the adenoviral vector as compared to the limited host cell range, the difficulty to concentrate and purify and the lower transfectivity of the retroviral vector. Further, *Zhang et al* clearly teach that the adenoviral vector is very effective not only in inhibiting tumor cell growth with wild-type p53 (e.g. column 14, lines 19-35), but also

broad gene transfer to cancer cells in general (column 20, lines 1-8). Thus, the Office has provided solid basis for reasons to combine the cited references.

Concerning the issue of the decreased p53 expression observed using the adenoviral vector, indeed, *Zhang et al* teach that p53 gene expression was rapidly decreased 5 days after the vector administration in the cited patent (column 14, lines 30-35). However, *Zhang et al* go on to teach that adenoviral vectors are nonintegrative in the genome, that the duration of gene expression depends on the type of the host cells, the type of genes transferred, and the relevant promoter used. *Zhang et al* particularly teach "THE SHORT-TERM HIGH LEVEL EXPRESSION OF THE WILD-TYPE P53 PROTEIN OBSERVED IN THE PRESENT STUDY MAY HAVE THE BENEFICIAL EFFECT OF REDUCING POSSIBLE SIDE EFFECTS ON NORMAL CELLS FOLLOWING IN VIVO TREATMENT" (column 14, lines 50-53). This beneficial effect is apparently applicable when it comes to using the adenoviral vector expressing TNF-α, because TNF-α is known to be a strong cytotoxic agent. Moreover, when it comes to killing tumor cells, a long-term effect is not always necessary and/or desirable. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Arguments concerning rejections of Claim 40 under 35 U.S.C. § 112, 1st paragraph, New Matter.

The appellant argues that example VI discloses a total dose of 50-70 Gy in page 42, thus the subject matter is adequately described in the specification. The appellant further argues that claim 40 conveys the meaning of the disclosure to the ordinary skill

in a manner close enough to the precise language of the specification as to not add new matter. The Appellant further cites the decisions of the Board and Court arguing the claim language need not mirror the language of the specification *in ipsis verbis* citing *In re Wright* and *Freerdson v. Gass*.

In response, it is noted in *In re Wright*, the court determined that the original specification for method of forming images using photosensitive microcapsules supports amended language of claims requiring that microcapsules be "not permanently fixed" to underlying surface, since specification describes removal of microcapsules from surface and warns that capsules not be disturbed prior to formation of image, which unequivocally teaches absence of permanently fixed microcapsules. This differs from instant case, wherein the specification teaches a total dosage of 50-70Gy that may apply over a period of more than 25 days at a daily dose of 2Gy, whereas the claim encompasses applying 50-70 Gy to a patient at once. Thus, this court decision does not support appellant's argument.

As to the *Freerdson v. Gass,* which indicates upfront, that foreign application for chemical patent relied upon for priority under 35 USC 119 need not describe, *in ipsis verbis,* chemical species within scope of interference count in order to comply with description requirement of 35 USC 112, first paragraph. However, a closer look of the decision would find that the court indicates, the question of whether an application contains a sufficient written description for "A COMPOUND WHICH IS NOT SPECIFICALLY DISCLOSED BUT WHICH IS AMONG THOSE SUGGESTED BY GENERAL LANGUAGE IN THE APPLICATION MUST BE DECIDED ON ITS OWN FACTS" (page 2011). The court then concluded "IN OUR VIEW,

THE SWISS APPLICATION (the aforementioned "foreign application") DOES NOT REASONABLY LEAD ONE OF ORDINARY SKILL TO ANY OF THE THREE AFOREMENTIONED BENZENESULFONAMIDE COMPOUNDS OF THE COUNT, I.E., DOES NOT REASONABLY CONVEY TO THOSE SKILLED IN THE ART THAT GASS HAD POSSESSION OF ANY OF THE THREE" (part II of the decision, emphasis and notation added). Thus, this court decision does not support appellant's argument.

Appellant is reminded that claims must, under modern claim practice, stand alone to define invention, since, in patentability context, claims are to be given their broadest reasonable interpretations, and since limitations are not to be read into claims from specification. *In re Van Guens*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

It is noted that appellant has attempted to amend claim 40 adding the word "total" in claim language in a response after final rejection submitted on April 2, 2003. This amendment was not entered because of the amendment to claim 29, but it would have been entered if only claim 40 be amended.

In conclusion, the Office has properly applied the methodology for determining whether a new matter is introduced into the disclosure as set forth under 35 U.S.C. § 112, 1st paragraph; and established that a new matter was introduced into the disclosure by the submission of claim 40 in November 2002. The Office has also properly applied the test for obviousness set forth in *Gramham v. John Deere Company*, and established a *prima facie* case of obviousness over claims 29 and 37 based on the teachings of *Zhang et al.* in view of *Walther et al.*

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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January 7, 2005

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